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DOI: <https://doi.org/10.1111/ceo.13949>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-209829>

Journal Article

Published Version



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Originally published at:

Nguyen, Vuong; Barthelmes, Daniel; Gillies, Mark C (2021). Neovascular age-related macular degeneration: A review of findings from the real-world Fight Retinal Blindness! registry. *Clinical Experimental Ophthalmology*, 49(7):652-663.

DOI: <https://doi.org/10.1111/ceo.13949>

Neovascular age-related macular degeneration: A review of findings from the real-world Fight Retinal Blindness! registry

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Funding information

Bayer and Novartis; Macular Disease Foundation Australia; the Australian National Health and Medical Research Council; RANZCO Eye Foundation

Abstract

The use of vascular endothelial growth factor (VEGF) inhibitors has revolutionised the treatment of neovascular age-related macular degeneration (nAMD) since the pivotal Phase III studies demonstrated their efficacy more than 10 years ago. The Fight Retinal Blindness! project was developed to track the treatment outcomes of patients with nAMD in real-world practice. Data from this registry have been used to answer several clinically relevant questions related to the treatment of nAMD including the effect of under-treatment, the comparative effectiveness of different anti-vascular endothelial growth factor agents, long-term treatment outcomes, identifying optimal treatment regimens and the rate and outcomes of rare adverse events. Observational studies are a valuable complement to the shortcomings of clinical trials and a combination of data from real-world settings and clinical trials are necessary to provide evidence on how to achieve the best outcomes for individual patients with nAMD.

KEYWORDS

disease registry, neovascular age-related macular degeneration, real-world evidence, vascular endothelial growth factor inhibitors

1 | INTRODUCTION

We are all fortunate that ways to treat neovascular age-related macular degeneration (nAMD), which at least previously was one of the commonest causes of blindness, have been discovered in our lifetimes. Rates of nAMD may be reduced by public health campaigns directed at its major environmental risk factor, cigarette smoking, but these can only be partially effective since it is estimated that the cause of the condition is 70% genetic.^{1,2} The Fight Retinal Blindness! (FRB!) project was developed to track

different regimens used for vascular endothelial growth factor (VEGF) inhibitors to identify which work best in different aspects of 'real-world' clinical practice.

2 | PHASE IV STUDIES AND REAL-WORLD EVIDENCE

The post-marketing surveillance of interventions that Phase IV studies provide forms a crucial piece of evidence when evaluating treatments and interventions alongside

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'efficacy' data from Phase III clinical trials.^{3,4} Phase IV studies serve three broad functions: (1) to monitor the safety of new interventions in large populations, particularly including specific groups not represented in clinical trials, (2) to determine the 'effectiveness' of interventions in routine clinical practice, and (3) to assess new ways to use approved products for new indications.³ These observational, non-interventional studies rely on the use of 'real-world evidence' (RWE). RWE refers to the information on health care from non-clinical trial settings such as electronic health records (EHR), claims and billing data, product and disease registries and data from personal devices and health applications.⁵ Such data from real-world settings have become increasingly important with the transition of the healthcare system towards evidence-based practice.

Randomised clinical trials (RCTs) remain the gold standard for testing new interventions but have a number of limitations, which RWE is better suited to address. RCTs often have strict selection criteria so their results cannot be generalised to the broader population seen in practice, including children, pregnant women, the elderly and those with co-morbidities.^{3,6} In contrast, RWE monitors outcomes for all patients receiving treatment for a condition, giving it greater external validity and relevance for key stakeholders such as patients, clinicians, regulators and reimbursement committees.^{7,8} Additionally, the large sample sizes and lower cost of collecting real-world data make it ideal for detecting rare adverse events and assessing long-term safety and outcomes which would not be feasible for a RCT.^{4,6,8} Many sources of real-world data are obtained as part of standard procedures (e.g., EHR and claims data) such that monitoring of safety and treatment outcomes can continue long after drugs have been approved for use. However, there are many limitations of real-world data including lack of standardised fields, lack of randomisation in comparative analyses resulting in selection bias and generally lower quality, more incomplete data. Importantly, such data are not collected for the purpose of answering specific hypotheses or research questions.^{4,6} Special care must therefore be taken when analysing and interpreting RWE.

The importance of real-world data and limitations of relying strictly on evidence from RCTs for the treatment of nAMD are evident. Early clinical trials of VEGF inhibitors for nAMD showed remarkable gains in vision ranging from 6.5 to 10.7 letters after 2 years of treatment every 4 weeks.^{9,10} However, these results could not be replicated in routine clinical practice as the burden of monthly anti-VEGF injections was not practical for most patients, resulting in fewer injections and worse outcomes.¹¹⁻¹⁶ These real-world studies, which identified

previously unrecognised shortfalls in the delivery of anti-VEGF treatment for nAMD, prompted a shift towards individualised treatment regimens such as pro re nata (PRN) and treat-and-extend (T&E) that could reduce the treatment burden without sacrificing visual outcomes.¹⁷

3 | FRB! REGISTRY

The FRB! registry is the flagship module of the Save Sight Registries (SSR; <http://savesightregistries.org/>) that specialises in tracking outcomes of retinal diseases with audits for nAMD, choroidal neovascularisation (CNV) other than nAMD, diabetic macular oedema and retinal vein occlusion. The FRB! registry, established in 2009, was designed as an online web-based tool to collect accurate, standardised, high-quality data from routine clinical practice, thereby distinguishing itself from other sources of real-world data.¹⁸ Analyses of FRB! data have addressed many clinically relevant issues in treating nAMD in routine clinical practice, most of which will be discussed in this review. Other modules in the SSR include Fight Corneal Blindness!, Fight Glaucoma Blindness and Fight Tumour Blindness!, which generally follow the same structure.

Data are entered when treatment is started and then at each clinical visit by the treating clinician or their assistant. Treatment decisions, including choice of drug, regimen and re-treatment criteria are at the discretion of the clinician in consultation with the patient, with no direction by the registry investigators, reflecting routine clinical practice. The choice of data fields was determined by a Steering Committee of retinal experts, and guided by parsimony, validity and focus on tracking relevant outcomes and emerging treatments in routine clinical practice. Also taken into consideration was the International Consortium of Healthcare Outcomes Measures (ICHOM) minimum set of standard outcome measures for macular degeneration of which the FRB! registry is currently compliant for nAMD.¹⁹ The full list of data fields recorded for the nAMD audit is provided in Table 1.

A major concern of the utility of registries for research is they are limited by the quality of the data which are rarely validated.²⁰ To address this, the FRB! registry has quality assurance measures built into the system to ensure that data are verified and are high-quality. Data can only be 'Saved' if not all the mandatory data are available or entered. The visit can only be 'Finalised' when all mandatory fields have been filled eliminating the possibility of missing data. This validation process also confirms all values are within predetermined ranges. Only finalised data are available for analysis. Categorical data such as angiographic lesion type are entered via a drop-down

TABLE 1 List of data fields collected for the nAMD audit of the FRB! registry

Field	Description	Visit type	Mandatory
Gender	Gender of patient	Baseline only	Yes ^a
Year of birth	Patient year of birth	Baseline only	Yes
Ethnicity	Ethnicity of patient	Baseline only	No ^a
Smoking status	Smoker, ex-smoker or non-smoker	Baseline only	No ^a
Postcode	Postcode of patient	Baseline only	No
Angiographic lesion type	Lesion classification using fluorescein angiography and/or optical coherence tomography, judged by treating clinician	Baseline only	Yes ^a
Previous treatment	Pre-treatment status of the patient	Baseline only	Yes
Ocular conditions	Other relevant ocular conditions that may affect vision such as glaucoma or cataract	Baseline only	Yes
Date of visit	Date of patient visit	Baseline and follow-up	Yes
Treatment	Treatment administered for that visit if any	Baseline and follow-up	Yes
Visual acuity	Number of letters read on a logMAR scale. Best of uncorrected, corrected or pinhole. May be entered in Snellen	Baseline and follow-up	Yes
Intraocular pressure	Intraocular pressure in mmHg	Baseline and follow-up	No
CNV activity	Lesion activity status graded as inactive, active with subretinal fluid only, or active with any combination of fluid excluding subretinal fluid only	Baseline and follow-up	Yes
Macular atrophy	Presence/absence and location of macular atrophy	Baseline and follow-up	Yes
Subretinal fibrosis	Presence/absence and location of subretinal fibrosis	Baseline and follow-up	
Adverse events	Treatment complications	Follow-up only	Yes
Ocular events	Other procedures given not directly related to treatment for nAMD such as cataract extraction or vitrectomy	Follow-up only	Yes
Discontinuation	Reason for discontinuation of patient from database, including non-treatment related reasons such as death	Follow-up only	No

Abbreviations: CNV, choroidal neovascularisation; FRB!, Fight Retinal Blindness!; nAMD, neovascular age-related macular degeneration.

^aOption to select undisclosed or unknown even if mandatory.

menu of pre-specified options instead of free text, which is avoided throughout. Additionally, a data-quality review was undertaken on a random subset of patients from clinicians who agreed to participate in the review.²¹ An independent assessor was sent to the clinician's practices to verify that the source data entered into the EHR matched the data entered into the FRB! registry. There was an overall error rate of 3.5%, with visual acuity (VA) being the most error-prone data field at 5.1% due to incorrect conversions from Snellen to logMAR. The FRB! registry has since allowed clinicians to enter VA as Snellen with the registry automatically converting it to logMAR to reduce these errors. A possible concern was the high rate of missed visits (10.2%) that was identified. Such patients with an unacceptably high rate of missed visits have generally been excluded from FRB! analyses in the selection criteria but ideally such data would be present.

As of 1 March 2021, the SSR contained data on more than 40 000 eyes from 28 000 patients and has

700 clinicians participating spanning 23 countries across Europe, Asia, Africa and the Pacific. This includes 29 290 eyes from 513 clinicians participating in the FRB! registries.

4 | KEY FINDINGS FROM THE FRB! REGISTRY

4.1 | Short- and long-term outcomes from RWE

The FRB! investigators provided the first report of 12-month outcomes of intravitreal therapy for nAMD in Australia using real-world data. These outcomes were among the best in the world at the time, with a mean gain of +4.7 letters after 12 months.²² In contrast, other real-world studies reported either stabilisation (i.e., no change from baseline),^{11,13} or much lower gains in vision



at 12 months.^{12,14,16} The superior outcomes found in Australia were almost certainly due to the higher mean of 7 injections compared with the 3–5 injections administered elsewhere. A follow-up FRB! analysis used a ‘matched’ cohort with the same inclusion criteria as the landmark Minimally Classic/Occult Trial of Anti-VEGF Antibody Ranibizumab (MARINA) clinical trial, and reported a mean gain of +5.5 letters.^{9,23} Although these real-world results were still lower than the RCTs, they were nonetheless reassuring and indicated VEGF inhibitors could achieve good outcomes in routine clinical practice without the need for monthly injections.

Reports of long-term outcomes of treatment are still limited even as many patients have been treated with VEGF inhibitors for over 10 years, which is much longer than the 2-year outcomes reported by the pivotal MARINA and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) clinical trials in 2006.^{9,24} An FRB! analysis in 2015 evaluated long-term outcomes of nAMD in 1212 eyes, with 549 completing 5 years of follow-up, representing the largest published set of long-term data available at the time.²⁵ Good outcomes were reported, with vision remaining stable for approximately 5 years although more than half of patients were lost to follow-up. The Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials (SEVEN-UP) study, which provided the only other long-term data available at the time, reported a mean vision loss of 8.6 letters at 7 years with only half as many injections as the FRB! cohort.²⁶ The Comparison of Age-related Macular Degeneration Treatment Trials (CATT) published later reported vision loss at 5 years, again with fewer injections.²⁷ Other factors that may have contributed to the better outcomes in the FRB! registry include differences in baseline vision, demographics and the treatment regimen with a treat and extend regimen likely to have been used by the FRB! practitioners and PRN approach by the other studies.²⁸

The first 10-year outcomes data on VEGF inhibitors for nAMD were published using data from the FRB! registry in 2020.²⁹ Eyes completing 10 years of continuous treatment in Australia and New Zealand had reasonably good outcomes with a mean loss of just 0.9 letters, in contrast to the Swiss cohort who lost a mean of 14.9 letters. The higher median number of injections in the Australia and New Zealand cohort (53 vs. 42 over 10 years) likely explained most of the difference between regions. This was despite a transition towards more intensive treatment in the Swiss cohort in later years, likely when evidence of poorer real-world outcomes from under-treatment became widespread. Subretinal fibrosis and

macular atrophy were the most common causes of long-term vision loss but, importantly, they did not develop universally in eyes receiving treatment for 10 or more years. A separate analysis of 10-year outcomes in France, also using FRB! registry data, had comparatively worse outcomes with a loss of 18 letters after a median of only 27.5 injections over 10 years.³⁰ A number of 10-year follow-up studies have since been published, confirming the relationship between injection frequency and that vision can be maintained at 10 years with ongoing treatment.^{31,32}

Overall, the FRB! registry presented an optimistic prognosis of real-world outcomes compared with other early observational studies, both short- and long-term. Australian patients may do well because the drugs are reimbursed without restriction and there enough practitioners who are adequately reimbursed to do the necessary number of injections. Beyond the need for more frequent treatment, further analyses into the possible causes and predictive factors of poor outcomes, including macular atrophy and subretinal fibrosis, may improve further the long-term outcomes of patients with nAMD.

4.2 | Variable dosing regimens

The variable T&E regimen attempts to balance maximising visual outcomes while reducing treatment frequency, by gradually extending the intervals between treatments while keeping the CNV lesion inactive and reducing the interval when it is active.³³ It presumes that the lesion will always reactivate, and it aims to give the next treatment just before that event. Unlike PRN, another variable regimen, T&E does not require monthly monitoring visits thus reducing the burden of visits although both generally begin with monthly dosing until the lesion becomes inactive. The FRB! investigators analysed the outcomes of T&E using ranibizumab and reported a mean vision gain of +5.3 letters at 2 years with a mean of 13 injections over 14.8 visits, effectively reducing the treatment frequency by nearly half that of a monthly regimen without monitoring visits while still achieving good outcomes.³⁴ A subsequent FRB! analysis of T&E using aflibercept similarly found good outcomes, a mean gain of +6 letters after 2 years with a mean of 13.6 injections.³⁵ Further evidence, including a meta-analysis and systematic review, indicated that T&E achieved better outcomes than PRN.^{15,17,36,37}

The T&E regimen consists of an induction phase, with monthly treatment intervals until the CNV lesion becomes inactive, followed by the maintenance phase in which treatment intervals are extended as long as the CNV lesion is inactive. Despite overwhelming evidence

of the efficacy of T&E, there were still many uncertainties and variations in management decisions, particularly during the maintenance phase. The FRB! registry gave a detailed description of patterns and outcomes during both phases of T&E to provide clinicians with further guidance.^{38,39} The median duration of the induction phase was reported to be 15 weeks, with 61% of CNV lesions becoming inactive with just 1–3 injections.³⁸ Interestingly, lesions induced with treatments at intervals exceeding 5 weeks required disproportionately more time and injections to become inactive, emphasising the importance of maintaining monthly treatment intervals early on. During the maintenance phase, treatment intervals were gradually extended before stabilising after 12 months, with most lesions settling at approximately 8-weekly intervals.³⁹ Of note, there was a substantial risk of lesion re-activation when treatment intervals exceeded 12 weeks suggesting that 3 monthly is a reasonable cap for extending intervals.

Variants of the T&E regimen continued to evolve in routine clinical practice amidst the difficulty of maintaining long-term treatment adherence and concerns regarding the risk of developing macular atrophy. Reports of a ‘treat-extend-stop’ variant were published, raising the possibility that some patients may be able to stop treatment altogether.^{40,41} An FRB! analysis investigated the outcomes of eyes in which treatment suspension, defined as ≥ 3 months of documented lesion inactivity with no treatment unless the lesion re-activated, was attempted.⁴² Approximately 41% of eyes that suspended treatment re-activated within the first year, increasing to 79% by the fifth year. Risks of re-activation were reduced in patients with poor vision or if they had been treated for at least 3 years prior to suspension. Vision that was lost due to re-activation was not recovered despite resuming treatment. Thus the decision to suspend treatment must be balanced against the possibility of irreversible vision loss which for some clinicians may be too risky.⁴³

4.3 | Comparative efficacy of ranibizumab and aflibercept

Bi-monthly aflibercept was found to be equivalent to monthly ranibizumab in the Phase III clinical trial, suggesting that it might have a longer duration of action.⁴⁴ The FRB! investigators directly compared VA and injection frequency outcomes between ranibizumab and aflibercept in routine clinical practice.⁴⁵ Visual outcomes at 12 months did not differ significantly between the two drugs (adjusted mean [95% CI] VA change +4.9 [1.5, 8.3] letters for aflibercept vs. +3.0 [−0.2, 6.3] letters

for ranibizumab; $p = 0.26$). There was also no evidence that aflibercept was injected less frequently than ranibizumab in real-world practice (mean 8.0 injections aflibercept for vs. 8.1 for ranibizumab), possibly due to the predominant use of T&E since the treatment intervals were extended regardless of drug choice. These findings have since been replicated in a RCT and observational studies.^{46,47} A follow-up comparison by the FRB! investigators extended the analysis to 36 months and again found no difference in visual outcomes or treatment frequency between ranibizumab and aflibercept.⁴⁸ Thus far, the FRB! registry has produced the longest and only 36-month comparison between these two drugs in real-world practice.

As the treatment effect of anti-VEGF injections for nAMD tends to be most pronounced after the first injection,^{24,49} a 4-week analysis was reasoned to offer the purest indication of the relative efficacy of each drug with fewer confounders such as treatment regimen and patient dropout.⁵⁰ A sub-analysis of 4 week results in the Comparison of Ranibizumab and Aflibercept for the Development of Geographic Atrophy in (Wet) AMD Patients (RIVAL) clinical trial reported more eyes receiving aflibercept lost vision 4 weeks after the first injection.⁴⁷ This result was not confirmed by the FRB! analysis, with an adjusted mean (95% CI) VA change of +3.5 (2.6, 4.4) letters for aflibercept and +3.6 (2.9, 4.3) letters for ranibizumab 4 weeks after the first injection in treatment-naïve eyes.⁵⁰ It appears that change in VA after the first injection for nAMD is more likely to be driven more by baseline characteristics, such as age, baseline VA and lesion characteristics, than by the drug.

4.4 | Fluid management

Treatment decisions under the PRN or T&E regimens are largely determined by the activity of the CNV lesion, indicated mainly by the presence of subretinal fluid (SRFL) or intraretinal fluid (IRFL), with the goal of keeping the lesion inactive with the fewest injections.^{17,33} Eyes with chronically active lesions generally receive monthly treatment under the guidelines of PRN or T&E. However, few data are available on the outcomes of persistent lesion activity to assess whether monthly injections are necessary in these eyes. Interestingly, an FRB! analysis investigating the 12-month outcomes found that persistently active eyes (CNV lesion graded as active at every visit) achieved a similar mean VA gain (+5.5 letters) with a similar mean number of injections (8.3) to those with less active lesions (+6.2 to +8.3 letters, 7.7 to 8.5 injections for the three remaining quartiles of lesion activity).⁵¹ Although these data hinted at the possibility



that fluid could be tolerated to an extent, the long-term effects of chronic lesion activity were still unknown.

There has since been some evidence that a degree of fluid may be tolerated, particularly SRFL which could protect against the development of macular atrophy.⁵²⁻⁵⁵ The development of macular atrophy and its possible link to treatment with VEGF inhibitors has been a growing concern given it is one of the main causes of irreversible long-term vision loss.^{25,29,55,56} An FRB! analysis reported the 5-year prevalence of macular atrophy at 42% and 48% at 9 years, with the strongest risk factor for atrophy being the proportion of visits in which the lesion was graded inactive (adjusted odds ratio 3.72 for the highest vs. lowest quartile of inactive gradings).⁵⁷ These results support the hypothesis that fluid may protect against the development of atrophy in the long-term, contradicting the goals of PRN and T&E to keep the CNV lesion inactive. The prevalence of macular atrophy also increased with the number of anti-VEGF injections, but whether the injections were the direct cause of atrophy or whether it was simply the natural history of AMD could not be determined.

The other major cause of long-term vision loss is subretinal fibrosis which is also untreatable and irreversible.^{27,29} In contrast to macular atrophy, the presence of fluid has been identified as a potential risk factor for the development of subretinal fibrosis.^{58,59} This idea was again supported by FRB! data, with a higher proportion of visits with active CNV associated with a greater risk of developing subretinal fibrosis (adjusted odds ratio 1.58 for the highest vs. lowest tertile of activity).⁶⁰ The prevalence of subretinal fibrosis was reported to be approximately 50% after 10 years of treatment, similar to the prevalence of macular atrophy.

This presents a dilemma for clinicians who wish to preserve long-term vision, since too little fluid may increase the risk of macular atrophy whereas too much fluid may increase the risk of subretinal fibrosis. The optimal approach appears to be to tolerate some retinal fluid, allowing for an intermediate level of fluid for the best long-term outcomes. An FRB! analysis of the 5-year outcomes by lesion activity, a follow-up of the analysis of 12-month outcomes of persistently active lesions, sought to investigate this hypothesis (unpublished data). This analysis indeed found that eyes in the highest tertile of disease activity (most active) had the worst outcomes at 5 years, with an adjusted mean (95% CI) VA change of -2.5 (-4.2 , -1.3) letters, followed by the lowest tertile (least active, -0.5 [-1.8 , 1.1] letters), with the middle tertile (moderately active) achieving the best outcomes ($+1.8$ [0.2 , 3.4] letters). Additionally, the percentage of eyes with macular atrophy decreased with activity (56%, 47% and 26% in the low, moderate and high tertiles of

activity respectively) while subretinal fibrosis increased with activity (27%, 36% and 42%).

These data present a compelling narrative regarding the importance of appropriate fluid management to preserve long-term vision. However, a major limitation in the two analyses just described was the lack of distinction between SRFL and intraretinal fluid (IRFL). Increasingly, it appears the location of the fluid is important in the decision to treat or tolerate fluid.⁵² While there is evidence that SRFL may be protective against atrophy and tolerated to an extent,^{52,55} IRFL has been reported to be associated with poorer visual outcomes and an increased risk of MA.^{55,61,62} Since 2017 onwards, clinicians in the FRB! registry were required to grade active lesions being either 'active SRFL only' or 'active with any combination of fluid excluding SRFL only'. A 12-month FRB! analysis utilising these new gradings grouped eyes based on whether they were mostly inactive, mostly active with SRFL only or mostly active with non-SRFL only (i.e., IRFL).⁶³ It found that eyes that were mostly active with SRFL only achieved similar mean (95% CI) adjusted VA gain ($+7.5$ [5.6 , 9.4] letters) to those that were mostly inactive ($+7.6$ [5.7 , 9.6] letters) while those that were mostly active with non-SRFL only gained the least ($+3.6$ [1.9 , 5.3] letters). This analysis confirmed the results of the 24-month FLUID RCT which also reported good outcomes when SRFL was tolerated.⁵² Longer-term data will be needed to determine in more detail the relationship between IRFL, SRFL and the development of macular atrophy and subretinal fibrosis. Regardless, optimal application of PRN and T&E in the long-term will likely involve tolerating some degree of fluid, most likely SRFL.

4.5 | Poor outcomes and adverse events

Despite the effectiveness of anti-VEGF for most eyes with nAMD, some respond poorly to treatment with major clinical trials reporting a loss of ≥ 15 letters in approximately 4%–6% of eyes at 12 months and 8%–10% at 24 months.^{9,10} Poor long-term outcomes are commonly due to macular atrophy or subretinal fibrosis but this does not account for all causes of long-term vision loss.^{25,29} An FRB! analysis detailing the incidence, characteristics and factors that contribute to vision loss over 5 years reported an estimated 23% of eyes had a sustained loss of ≥ 15 letters at 5 years (loss without recovery by the endpoint), with 11% losing ≥ 30 letters.⁶⁴ Older age, fewer injections (under-treatment) and eyes with the highest proportion of visits with active CNV were associated with sustained vision loss. Another FRB! analysis that separately analysed smoking status as a potential risk factor for poor outcomes found it was associated with a lower



adjusted mean (95% CI) VA change at 12 months (+4.6 [1.5, 7.8] letters) compared with ex-smokers (+5.9 [3.4, 8.3] letters) and non-smokers (+8.0 [6.0, 10.0] letters).⁶⁵

Although macular atrophy and subretinal fibrosis are the most common causes of poor long-term outcomes for nAMD patients, adverse ocular events specifically associated with anti-VEGF therapy are quite rare.^{8,66} The rarity of these events makes real-world data more suited to monitoring their rate and subsequent than RCTs. One of the more severe complications of anti-VEGF treatment is endophthalmitis, which may be infectious or non-infectious. Data from the FRB! registry estimated the incidence of endophthalmitis was low and did not increase with each successive injection, with a per injection risk of infectious endophthalmitis at 0.020% and 0.012% for non-infectious endophthalmitis.⁶⁷ These closely approximated the results from a meta-analysis of real-world outcomes which estimated the rate at 0.026%.¹⁵ However, the FRB! data also suggested non-infectious endophthalmitis was more common with the unlicensed anti-VEGF agent, bevacizumab (0.081%), compared with ranibizumab (0.005%) and aflibercept (no cases recorded). Approximately three quarters of infectious and two thirds of non-infectious endophthalmitis cases recovered vision to within 10 letters of their pre-endophthalmitis VA after having lost approximately a mean of 20 letters of vision. These outcomes were slightly better than previous reports⁶⁸ and may have been because treatment intensity was maintained. Continuing anti-VEGF treatment after an attack of endophthalmitis has resolved therefore seems to be of some benefit.

Treatment with anti-VEGF may also increase the risk of retinal pigment epithelium (RPE) tears.^{69,70} Although continued treatment with anti-VEGF after the RPE tear showed beneficial outcomes,⁶⁹ reports of long-term outcomes have been less encouraging despite persistent treatment.⁷¹ An FRB! analysis focusing on the visual outcomes of RPE tears identified two distinct responses based on when the tear occurred and the response to treatment prior to the tear.⁷² Eyes which had an early tear occurring before 6 months (approximately 70% of the tears recorded) had experienced a very strong improvement in vision prior to the tear. This positive response may be associated with a greater tendency for the CNV to shrink, which causes the tear.⁷⁰ Vision loss due to these 'early' tears recovered quite well, reaching levels comparable to matched controls that did not develop a tear. When tears occurred late, after 6 months of treatment, the neovascular complex is less likely to shrink.⁷³ VA in these eyes with 'late' tears was in decline even prior to the tear so it is possible that the tear was due to progressive growth of the CNV and the consequent atrophic damage to the RPE in eyes that were already not

responding well to treatment. The long-term prognosis of eyes affected by RPE tears may therefore be related more to the patient's response to therapy rather than to the tear itself.

4.6 | Angiographic lesion subtypes

The Macular Photocoagulation Study in 1991 characterised lesion subtypes based on fluorescein angiography as 'classic', or well-defined CNV, and 'occult', or poorly defined, CNV.⁷⁴ This classification scheme was considered clinically important since the natural history and response to treatments available at the time, particularly photodynamic therapy (PDT) with verteporfin, varied between the CNV types.⁷⁵ An updated classification scheme using fluorescein angiography and ocular coherence tomography was proposed which identified Type 1 lesions (generally occult), Type 2 lesions (generally classic) and Type 3 which corresponded to retinal angiomatous proliferation (RAP).⁷⁶ While the Macular Photocoagulation Study classification scheme was subsequently used when selecting and monitoring eligible patients for RCTs for anti-VEGF,^{9,24} its clinical relevance once anti-VEGF became the first-line treatment had not been questioned. A 5-year FRB! analysis compared Type 1 and Type 2 lesions to assess whether there were differences in real-world visual outcomes or treatment intensity when treated with anti-VEGF injections. Mean baseline vision was higher in occult CNVs (56.9 letters) than the minimally (52.9 letters) and predominantly classic (49.1 letters) variants and was still higher at 5 years. However, lesion type did not affect 5-year VA improvements after multivariate adjustment for age, lesion size and baseline vision. There was also no difference in injection frequencies with Type 1 and Type 2 lesions receiving 29–30 injections over 5 years. Thus, the classification of CNV lesions into Type 1 and Type 2 may be irrelevant to clinicians and patient management when eyes are treated with intravitreal therapy.

RAP lesions were thought to have a poorer response to treatment and worse functional outcomes than Type 1 and Type 2 lesions when they were first described.⁷⁷ A sub-analysis of RAP lesions in the CATT clinical trial, however, reported similar outcomes at 2 years compared with other lesion types.⁷⁸ The lack of large studies or real-world data comparing RAPs with non-RAP lesions may have prolonged the perception that RAPs were more difficult to treat. An FRB! analysis compared the 24-month outcomes of RAPs with a control cohort of other lesion types matched on baseline vision, year of treatment initiation and anti-VEGF agent used. RAP lesions actually had better mean (95% CI) visual



outcomes at 24 months (+5.1 [2.8, 7.3] letters) than the matched controls (+2.5 [1.0, 4.0] letters).⁷⁹ The significantly smaller lesion size characteristic of RAP lesions, along with the lower levels of lesion activity observed may have contributed to these better outcomes. These data confirm the results from the CATT sub-analysis and adds to the body of evidence that anti-VEGF is just as efficacious for RAP lesions as it is for other forms of sub-retinal neovascularisation.

A unique variant of Type 1 choroidal neovascularisation is polypoidal choroidal neovascularisation (PCV), which is more commonly found among Asian populations than Caucasian populations.⁸⁰ Unlike other lesion subtypes, there is some evidence that the addition of PDT in combination with anti-VEGF achieves better outcomes than anti-VEGF monotherapy, however more data are required to confirm these results and data from routine clinical practice are lacking.^{81,82} Investigators from the FRB! registry identified patients with PCV lesions treated with either anti-VEGF monotherapy or combination anti-VEGF with PDT.⁸³ Eyes that received combination therapy in routine clinical practice presented with significantly lower baseline vision, possibly because PDT was only considered in more advanced cases or patients in Asia, where PDT is more commonly used, seek treatment later. However, mean (95% CI) visual outcomes at 12 months after multivariate adjustment were significantly better following combination therapy (+16.9 [10.6, 23.3] letters) than with anti-VEGF monotherapy (+8.2 [5.2, 11.3] letters). While previous RCTs comparing combination with anti-VEGF monotherapy used ranibizumab, PCV patients from the FRB! registry were mostly receiving unlicensed bevacizumab which was the predominant drug available in Singapore and New Zealand. Regardless, the FRB! study provides additional evidence for the use of combination anti-VEGF with PDF for patients diagnosed with PCV.

4.7 | International outcomes and audits

The international expansion of the FRB! registry has allowed participating counties to conduct audits into their own outcomes from routine clinical practice to benchmark outcomes, identify potential areas for improvement and highlight certain idiosyncrasies. Investigators from Spain were interested in comparing outcomes between study sites within the same hospital but utilising different treatment strategies, fixed bi-monthly with aflibercept and T&E.⁸⁴ No significant differences in visual outcomes were found but the individualised T&E approach was able to reduce the burden of treatment for many eyes. An analysis from France reported a modest mean (95% CI) gain in visual outcomes of +3.3 (0.7, 5.9)

letters at 12 months, comparatively lower than RCTs and previous FRB! reports, possibly due to the use of the PRN regimen.⁸⁵ Practitioners from the Netherlands, where bevacizumab is the first-line treatment according to the guidelines of the Dutch Ophthalmological Society, benchmarked their outcomes against a control cohort from Australia and Switzerland where ranibizumab or aflibercept were used.⁸⁶ They reported similar visual outcomes at 12, 24 and 36 months, albeit at the cost of significantly more injections, visits and switching to alternative VEGF inhibitors. Investigators from Singapore analysed the effects of delayed re-treatment of active disease in a large tertiary centre in Singapore, distinct from under-treatment traditionally defined as a low number of injections which does not necessarily consider disease activity.⁸⁷ They found that patients with delayed treatment of active disease had worse outcomes even when the absolute number of injections were similar, highlighting the importance of timely re-treatment of active disease with the possible exception of SRFL.

5 | FUTURE RESEARCH

FRB! investigators are committed to tracking the outcomes of new drugs as they are released for use in real-world practice. These drugs, such as brolucizumab and faricimab, achieved visual improvements for nAMD that were non-inferior to currently approved agents in the pivotal Phase III studies with more eyes able to be treated at 3 and 4 monthly intervals.^{88,89} Whether they also achieve this in real-world practice, where we anticipate that they will be administered according to a treat and extend regimen, will only be established by observational registries such as FRB!

The FRB! project has plans to offer its free software more widely, in keeping with its philosophy that tracking outcomes will drive better outcomes across the board. There are plans to make gains in Asia over the next 5 years similar to those that have been made in Europe over the last 5 years. A new module has recently been released to track the outcomes of people with uveitis while standard outcome sets for both inherited retinal diseases and retinopathy of prematurity have been identified.

One challenge for observational studies of retinal disease is to link automatically clinical outcome sets with images of the retina, such as ocular coherence tomography scans, which are an indispensable part of real-world care. This will facilitate studies that correlate function and outcomes with anatomical outcomes which lend themselves to analysis by artificial intelligence.

6 | CONCLUSIONS

RCTs only get us halfway there. If we want to get the best outcomes for our patients from new treatments, we also need to see the data from real world practice. This has been particularly the case for conditions such as nAMD, for which the pivotal clinical trials tend to use treatment regimens that practitioners and patients in real-world practice would mostly be unable to follow even if they wanted to. Observational studies are also essential to track outcomes over the lifetime of a patient, which clinical trials cannot do. The FRB! project has, along with other observational studies, helped to establish treatment regimens for routine clinical practice which are feasible and effective. Observational registries will continue to provide essential evidence for practice as the first generation of VEGF inhibitors come off patent and second generation agents, together with biosimilars, become available.

CONFLICT OF INTEREST

None declared.

FUNDING SOURCES

The FRB project has been supported by grants from the RANZCO Eye Foundation, the Australian National Health and Medical Research Council, the Macular Disease Foundation Australia and unrestricted grants from Bayer and Novartis.

FINANCIAL DISCLOSURE

Mark C. Gillies: Research funding and honour area for presentations at meetings and advisory boards for Bayer, Novartis and Roche. Consultant for Novelty-Nobility and OliX.

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How to cite this article: Nguyen V, Barthelmes D, Gillies MC. Neovascular age-related macular degeneration: A review of findings from the real-world Fight Retinal Blindness! registry. *Clin Experiment Ophthalmol*. 2021;49(7):652–663. <https://doi.org/10.1111/ceo.13949>